REMARKS

Allowable Subject Matter

Applicants gratefully acknowledge the Examiner's indication that the aminobenzofuran compounds of Group II are allowable.

Amendments

Claims 1, 3, 6, 8, 13, and 14 are amended to delete the non-elected subject matter of Formula I. Applicants reserve the right to file a divisional application directed to the cancelled subject matter.

Claims 1, 2 and 7 are amended to delete oxo as a heteroaryl substituent. Claim 8 is also amended to delete superfluous language. Claims 10-12 and 15 are cancelled. Claim 2 is amended to correct errors in punctuation. Claim 22 is amended to be directed to enhancing cognition. Claim 29 is amended to be in independent form. Claim 30 is amended to delete drug addiction andrphine dependence. These aspects are recited in new claim 52.

Claims 31-32 are cancelled. Claim 35 is amended to delete neurogenesis. Claim 36 is amended to correct a typographical error. Claim 36 is also amended to recite age-related cognitive decline. See original claium 27, which is now cancelled.

New claims 37-55 are directed to further aspects of applicants' invention and are supported throughout the disclosure. See, e.g., the original claims, page 15, lines 1-4, page 16, lines 10-18, page 17, line 20-page 18, line 20, page 19, lines 15-18, page 20, lines 1-12, page 29, lines 5-7, page 30, lines 17-21, page 32, lines 7-14, and page 33, lines 1-22.

Objection to Claims 1-9 and 11-36

As mentioned above, the claims are amended to delete non-elected subject matter, i.e. the compounds of Formula I. Withdrawal of the objection is respectfully requested.

Rejection under 35 USC §112, first paragraph

Claims 22-36 are rejected under 35 USC §112, first paragraph, as allegedly being nonenabled with respect to methods for treating psychosis, allergic or inflammatory disease, or neurodegeneration resulting from a disease or injury. This rejection is respectfully traversed.

Concerning the state of the art, the rejection argues that the pharmacological art involves screening, *in vitro* and *in vivo,* compounds, and there is no absolute predictability despite a high level of skill in the art. However, enablement under 35 USC 112, first paragraph, does not require absolute predictability. Moreover, as discussed in more detail below, the "state of the art" is that the art undeniably recognizes the use of PDE4 inhibitor compounds to treat inflammation and associated diseases, diseases involving decreased cAMP levels, psychosis, neurodegeneration, and to enhance cognition.

The rejection also asserts that the pharmacological art is generally considered to be unpredictable. But, the mere allegation that arts concerning physiological activity are generally unpredictable does not lead to a *per se* conclusion of undue experimentation, or lack of enablement.

An application disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance with the enabling requirement of the first paragraph 35 U.S.C. § 112, unless there is reason to doubt the objective truth of statements contained therein relied on for enabling support. *In re Brana, 51 F.3d 1560,* 34 USPQ2d 1436 (Fed. Cir. 1995). *Fiers v. Revel, 984 F.2d 1164,* 24 USPQ2d 1601 (Fed. Cir. 1993). Furthermore, as stated in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971), the PTO must have adequate support for its challenge to the credibility of applicants' statements of utility. See also *In re Bundy*, 209 USPQ 48 (CPA 1981).

Hence, to establish non-enablement, the rejection can not merely assert, for example, that the treatment of inflammation is non-enabled. Instead, the rejection must present reasons why one or ordinary skill in the art would doubt that inflammation can be treated using applicants' PDE4 inhibitor compounds, despite the fact that, as discussed

further below, the art clearly recognizes the use of PDE4 inhibitors to treat inflammation and associated diseases.

With regards to guidance, the rejection argues that there are no test data on PDE4 inhibition. However, it is by now well settled law that to establish the requisite objective enablement under the 35 USC 112, first paragraph, an applicants' disclosure is not required to present specific test results such as *in vivo* or *in vitro* test results. All that is required under the statute is objective enablement. See, e.g., *Marzocchi et al.*, at 369:

> The first paragraph of §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

The MPEP is also in agreement with the holding in *Marzocchi.* The MPEP states that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The test for enablement is not whether any experimentation is needed but whether or not that experimentation is undue. See, e.g., *In re Angstad*t, 190 USPQ 214, 219 (CCPA 1976) in which the art involved (catalysis) was acknowledged to be unpredictable. Even a considerable amount of experimentation, or complex experimentation, is permissible if it is routine. See, e.g., *Ex parte Jackson,* 217 USPQ 804, 807 (POBA 1982) and *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

Merely because it is alleged that a specific example of enzyme inhibition is not presented in the specification, one of ordinary skill in the art would not doubt the truth of the statements concerning, for example, the treatment of inflammation. As noted above, MPEP § 2164.02 states that compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. The nature of the invention and the state of the prior art demonstrate that applicants' specification provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention.

With respect to guidance, applicants' specification provides more than sufficient guidance with respect to dosages, formulations, modes of administration, and assays for

determining the relative amount of PDE4 inhibitory activity. See, e.g., pages 28-30, 34-35 and Examples 10, 11A, and 11B.

In the rejection, the Examiner argues that cancer is an inflammatory disease and that cancer therapy is highly unpredictable. Yet, as noted above, absolute predictability is not required under the statute. Moreover, method claims are inherently functional. In other words, the literal scope of the method claims encompass only embodiments that achieve the specified function. See, e.g., *In re Angstadt*, 190 USPQ 214 (CCPA 1976) and *Dinn-Nguyen et al.,* 181 USPQ 46 (CCPA 1974).

The arguments presented in the rejection do not establish any reason for one of ordinary skill in the art to doubt the statements of enablement in applicants' disclosure concerning treating inflammatory disease, especially since the use of PDE 4 inhibitors for treating inflammation is extremely well known in the art. For example, at page 34, lines 1-6 of the specification, applicants list some prior disclosures concerning anti-inflammatory activity of PDE 4 inhibitors. See, for example, US 5,814,651, already of record, which states the following at column 1, lines 31-51:

> Since the recognition that cyclic AMP is an intracellular second messenger (E. W. Sutherland, and T. W. Rall, Pharmacol. Rev., 1960, 12, 265), inhibition of the phosphodiesterases have been a target for modulation and, accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J. A. Beavo and D. H. Reifsnyder, TIPS, 1990, 11, 150), and their selective inhibition has led to improved drug therapy (C. D. Nicholson, R. A. Challiss and M. Shahid, TIPS, 1991, 12, 19). **More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator release** (M. W. Verghese et al., J. Mol. Cell Cardiol., 1989, 12 (Suppl. II), S 61) **and airway smooth muscle relaxation** (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donnell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). **Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway**

smooth muscle without causing cardiovascular effects or antiplatelet effects. (emphasis added)

Numerous other references of record show that the art unquestionably recognizes the use of PDE4 inhibitors in the types of methods recited in applicants' claims. The following is merely an exemplary list.

Marfat (WO 97/49702) discloses that PDE4 inhibition can lead to inhibition of inflammatory mediator response, and that PDE4 inhibitors have been found useful in the treatment of diabetes insipidus and central nervous disorders such as depression and multi-infarct dementia. See page 1, lines 15-32. See also WO 98/09961, pages 1-2.

Ina et al. (EP 0 994 100) discloses that PDE4 inhibitors are useful for treating inflammatory diseases and autoimmune diseases. See page 1, lines 18-24.

Freisen et al. discloses using PDE4 inhibitors for a variety diseases and conditions such as asthma, chronic bronchitis, chronic obstructive pulmonary disease, esoniophilic granuloma, psoriasis, endotoxic shock, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, , arterial restenosis, rheumatoid arthritis, and osteoarthritis, as well as cancer, depression, memory impairment, tumor growth, and cancerous invasion of normal tissues. See page 3, lines 7-27.

Braunlich et al. (WO 00/69841) discloses using PDE4 inhibitors for treating inflammatory and autoimmune disease. See, e.g., paragraph bridging pages 23-24.

Frenette et al. (WO 00/64874) discloses treating inflammatory diseases by a variety of mechanisms using PDE4 inhibitors, as well as the use of PDE4 inhibitors to prevent tumor growth and to counteract depression and memory impairment. See pages 11-12.

See also the numerous articles of record that demonstrate the use of the PDE4 inhibitor rolipram in improvement of memory, e.g., Zhang et al. (2000), Bach et al. (1999), Barad et al. (1998), and Egawa et al. (1997).

Other articles already of record discuss the well-established anti-inflammatory activity of PDE4 inhibitor compounds. For example, the 2000 article by Boichot et al. discloses:

> Among theses isoenzymes, type 4 PDE (PDE4) appears to be a molecular target for new anti-inflammatory drugs (Torphy, 1988). Indeed, PDE4 enzyme has a major cAMP-hydrolyzing activity in immune and anti-inflammatory cells (Tenor and Schudt, 1996), and the elevation of intracellular cAMP in these cell types reduces their activity and the release of inflammatory mediators (Alvarez et al., 1996). Moreover, the selective inhibition of PDE type 4 isoenzyme by PDE4 inhibitors leads to a marked anti-inflammatory activities in vitro and in vivo in several animal models (for a review, see Teixeira et al., 1997).

See also the article by Sawanishi et al. (1997)

To further demonstrate the art's well established recognition of the use of PDE4 inhibitors in the treatments recited in applicants' method claims, the following are excerpts from additional patent publications:

US 6,043,263: column 14, lines 33-50

> The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. **As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (namely of type IV), they are suitable** on the one hand as bronchial therapeutics (for the treatment of airway obstructions on account of their dilating but also on account of their respiratory rate- or respiratory drive-increasing action) and for the elimination of erectile dysfunction on account of the vasodilatory action, but on the other hand **especially for the treatment of disorders, in particular of inflammatory nature, e.g. of the airways (asthma prophylaxis)**, of the skin, **of the intestine, of the eyes and of the joints, which** are mediated by **mediators such as histamine, PAF (platelet-activating** factor), **arachidonic acid derivatives such as**

leukotrienes and prostaglandins, cytokines, interleukins, chemokines, alpha-, beta- and gamma-interferon, tumor necrosis factor (TNF) or oxygen radicals and proteases. (emphasis added)

US 6,294,564: column 18, line 38-coluim 19, line 13

On account of their PDE-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine and therapeutics, where they can be used, for example, **for the treatment and prophylaxis of the following illnesses: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of various origins** (bronchitis, allergic bronchitis, bronchial asthma, emphysema, COPD); **dermatoses (especially of proliferative, inflammatory and allergic type)** such as, for example, psoriasis (vulgaris), toxic and allergic contact eczema, atopic eczema, seborrhoeic eczema, lichen simplex, sunburn, pruritus in the anogenital area, alopecia areata, hypertrophic scars, discoid lupus erythematosus, follicular and wide-area pyodermias, endogenous and exogenous acne, acne rosacea and other proliferative, **inflammatory and allergic skin disorders;** disorders which are based on an excessive release of TNF and leukotrienes, e.g. disorders of the arthritis type (rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions), disorders of the immune system (AIDS, multiple sclerosis), graft-versus-host reactions, transplant rejection reactions, symptoms of shock [septic shock, endotoxin shock, gram-negative sepsis, toxic shock syndrome and ARDS (adult respiratory distress syndrome)], and **generalized inflammations in the gastrointestinal area** (Crohn's disease and ulcerative colitis); disorders which are based on allergic and/or chronic, faulty immunological reactions in the area of the upper airways (pharynx, nose) and the adjacent regions (paranasal sinuses, eyes), such as, for example, allergic rhinitis/sinusitis, chronic rhinitis/sinusitis, allergic conjunctivitis and nasal polyps; but also disorders of the heart which can be treated by PDE inhibitors, such as, for

example, cardiac insufficiency, or disorders which can be treated on account of the tissue-relaxant action of the PDE inhibitors, such as, for example, erectile dysfunction or colics of the kidneys and the ureters in connection with kidney stones. In addition, the compounds according to the invention can be employed for the treatment of diabetes insipidus and disorders in connection with disturbances of brain metabolism, such as, for example, cerebral senility, senile dementia (Alzheimer's dementia), multiinfarct dementia or alternatively disorders of the CNS, such as, for example, depressions or arteriosclerotic dementia. (emphasis added)

US 6,294,564: column 20, line 41-coluim 21, line 3

Substances which inhibit chemoluminescence and cytokine secretion and the secretion of inflammatory mediators on inflammatory cells, in particular neutrophilic and eosinophilic granulocytes, T lymphocytes, monocytes and macrophages, are those which inhibit PDE4. This isoenzyme of the phosphodiesterase families is particularly represented in granulocytes. Its inhibition leads to an increase in the intracellular cyclic AMP concentration and thus to the inhibition of cell activation. **PDE4 inhibition by the substances according to the invention is thus a central indicator of the suppression of inflammatory processes** (Giembycz MA, Could isoenzyme-selective phosphodiesterase inhibitors render bronchodilatory therapy redundant in the treatment of bronchial asthma?. Biochem Pharmacol 1992, 43, 2041-2051; Torphy TJ et al., Phosphodiesterase inhibitors: new opportunities for treatment of asthma. Thorax 1991, 46, 512-523; Schudt C et al., Zardaverine: a cyclic AMP PDE 3/4 inhibitor. In "New Drugs for Asthma Therapy", 379-402, Birkhauser Verlag Basle 1991; Schudt C et al., Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca; Naunyn-Schmiedebergs Arch Pharmacol 1991, 344, 682-690; Tenor H and Schudt C, Analysis of PDE isoenzyme profiles in cells and tissues by pharmacological methods. In "Phosphodiesterase

Inhibitors", 21-40, "The Handbook of Immunopharmacology", Academic Press, 1996; Hatzelmann A et al., Enzymatic and functional aspects of dual-selective PDE3/4-inhibitors. In "Phosphodiesterase Inhibitors", 147-160. "The Handbook of Immunopharmacology", Academic Press, 1996).

US 6,555,572: column 2, lines 21-40

For additional and more detailed discussion of PDE enzymes, including the history of their discovery, their characterization and classification, their in vivo activity, their inhibition by small organic molecules, and current clinical efforts directed to providing pharmaceutical compositions containing these small molecules, see, e.g., Bumouf, C. et al. "Phosphodiesterase 4 Inhibitors" Annual Reports in Medicinal Chemistry, Vol. 33, Chap. 10, pp 91-109, 1998 (Bristol, J. A., ed.); Essayan, D. M. "Cyclic Nucleotide Phosphodiesterase (PDE) Inhibitors and Immunomodulation" Biochemical Pharmacology 57:965-973, 1999; Souness, J. E. and Foster, M. "Potential of phospodiesterase type IV inhibitors in the treatment of rheumatoid arthritis" Idrugs 1(5):541-553, 1998; **Souness, J. E. et al. "Immunosuppressive and anti-inflammatory effect of cAMP phosphodiesterase (PDE) type 4 inhibitors" Immunopharmacology 47: 127-162, 2000**; and Torphy, T. J. "Phosphodiesterase Isozymes" Am J. Respir. Crit. Care Med. 157:351-370, 1998, as well as the numerous references cited in these articles. (emphasis added)

US 6,204,275: column 1, lines 34-48

The availability of PDE isotype selective inhibitors has enabled the role of PDEs in a variety of cell types to be investigated. **In particular it has been established that PDE IV controls the breakdown of cAMP in many inflammatory cells**, for example, basophils (Peachell P. T. et al., (1992) J. Immunol., 148: 2503-2510) and eosinophils (Dent G. et al., (1991) Br. J. Pharmacol., 103: 1339-1346) **and that inhibition of this**

isotype is associated with the inhibition of cell activation. Furthermore, elevation of cAMP in airway smooth muscle has a spasmolytic effect. Consequently PDE IV inhibitors are currently being developed as potential anti-inflammatory drugs particularly for the prophylaxis and treatment of asthma, by achieving both anti-inflammatory and bronchodilator effects. (emphasis added)

US 5,889,014: column 1, line 54- column 2, line 8

The structure-activity relationships (SAR) of isozyme-selective inhibitors has been discussed in detail, e.g., in the article of Theodore J. Torphy, et al., "Novel Phosphodiesterase Inhibitors For The Therapy Of Asthma", Drug News & Prospectives, 6(4) May 1993, pages 203-214. The PDE enzymes can be grouped into five families according to their specificity toward hydrolysis of cAMP or cGMP, their sensitivity to regulation by calcium, calmodulin or cGMP, and their selective inhibition by various compounds. PDE I is stimulated by Ca.sup.2+ /calmodulin. PDE II is cGMP-stimulated, and is found in the heart and adrenals. PDE III is cGMP-inhibited, and inhibition of this enzyme creates positive inotropic activity. **PDE IV is cAMP specific, and its inhibition causes airway relaxation, anti-inflammatory and ant-depressant activity.** PDE V appears to be important in regulating cGMP content in vascular smooth muscle, and therefore PDE V inhibitors may have cardiovascular activity. (emphasis added)

US 6,258,833: column 1, lines 6-17, and column 3, lines 44-57

The present invention relates to a series of compounds that are potent and selective inhibitors of cyclic adenosine 3',5'-monophosphate specific phosphodiesterase (cAMP specific PDE). **In particular, the present invention relates to a series of novel pyrrolidine compounds which are useful for inhibiting the function of cAMP specific PDE, in particular, PDE4, as well as methods of making the same, pharmaceutical**

compositions containing the same, and their use as therapeutic agents, for example, in treating inflammatory diseases and other diseases involving elevated levels of cytokines and proinflammatory mediators. (emphasis added)

Investigators have shown considerable interest in the use of PDE4 inhibitors as anti-inflammatory agents. **Early evidence indicates that PDE4 inhibition has beneficial effects on a variety of inflammatory cells such as monocytes, macrophages, T-cells of the Th-1 lineage, and granulocytes. The synthesis and/or release of many proinflammatory mediators, such as cytokines, lipid mediators, superoxide, and biogenic amines, such as histamine, have been attenuated in these cells by the action of PDE4 inhibitors.** The PDE4 inhibitors also affect other cellular functions including T-cell proliferation, granulocyte transmigration in response to chemotoxic substances, and integrity of endothelial cell junctions within the vasculature. (emphasis added)

US 5,124,455: column 1, lines 32-55

Cyclic AMP concentrations within the living cell are determined by both the rate of its synthesis by adenylate cyclase and the rate of its degradation by phosphodiesterases (PDEs). Thus, either stimulating adenylate cyclase or inhibiting PDEs in pulmonary tissues can result in anti-asthmatic activities. **This invention relates to compounds that inhibit a specific PDE, often called PDE IV, which selectively metabolizes cAMP** and which is insensitive to the modulatory effects of guanosine cyclic 3':5' monophosphate (cGMP) and calcium. This PDE is found in both respiratory smooth muscle and inflammatory cells, and has been demonstrated to be a principal regulator of cAMP in these tissues [see Torphy and Cieslinski, Molecular Pharmacology, 37, 206 (1990), and Dent et al., British Journal of Pharmacology, 90, 163P (1990)]. **Consequently, the compounds of the invention are bronchodilatory**

and antiinflamatory, and exhibit activity in animal models of allergic and nonallergic asthma. However, because the compounds of the invention have not been found to inhibit other forms of PDE, they are deemed to be more selective and safer anti-asthmatics than nonselective PDE inhibitors currently used for the treatment of asthma, such as theophylline.

See, also, the disclosure of Hagan et al. (US 2003/0187006) which recognizes the use of PDE4 inhibitors not only in the treatment of inflammatory diseases but, also in the enhancement of cognitive function. See, e.g., paragraphs [003] - [006].

See, also, for example, Takayama et al., US 6,136,810, which discloses pyrido[2,3-D]pyrimidine compounds as PDE4 inhibitors. At column 20, line 9 - column 21, line 48 US '810 lists conditions for which the compounds can be used, for example:

> The compounds of the present invention represented by the general formula (I) or pharmaceutically acceptable salts thereof are useful as medicines, because they have an excellent activity to inhibit type IV PDE, and the activity is selective for type IV PDE.
>
> In consequence, the compounds of the present invention can be used for the prevention or treatment of various diseases in which type IV PDE is concerned. The following exemplifies such a type of diseases.
>
> Respiratory diseases [e.g., bronchial asthma (including atopic asthma), chronic bronchitis, pneumonia, adult respiratory distress syndrome (ARDS) and the like],
>
> inflammatory diseases [e.g., atopic dermatitis, conjunctivitis, urticaria, acquired immunodeficiency syndrome (AIDS), keloid formation, rhinitis, iridocylitis, gingivitis, periodontitis, alveolar pyorrhea, gastritis, ulcerative colitis, Crohn disease, gastrointestinal ulcer, esophagitis, myositis, encephalitis (myasthenia gravis, multiple sclerosis and neuritis), hepatitis, cicatrization, nephritis (including proliferative nephritis), peritonitis, pleuritis, scleritis, scleroderma, burn injury and the like],

a systemic or local arthropathy (e.g., osteoarthrosis, gouty arthritis, chronic rheumatoid arthritis, malignant rheumatoid, psoriatic arthritis and the like),
proliferative diseases [e.g., malignant tumor, leukemia, proliferative dermatopathy (keratosis and various types of dermatitis), collagen disease and the like],
diseases related to nervous function abnormality (e.g., **learning, memory and cognition** disturbances related to nervous degeneration diseases such as Alzheimer disease, Parkinson disease and the like, multiple lateral sclerosis, senile dementia, amyotrophic lateral sclerosis, acute demyelinating neuritis, muscular dystrophy and the like),
diseases with mental function abnormality (e.g., manic-depressive psychosis, schizoid, anxiety, panic and the like),
(emphasis added)

See also, Man et al., US 6,911,464, which discloses N-alkyl-hydroxamic acid-isoindolyl compounds for use in the treatment of diseases associated with PDE4. At column 28, line 11 - column 29, line 39 US '464 discloses treatments using the PDE4 inhibitor compounds, for example:

The compounds of the invention are also useful for treating, preventing and managing all types of CNS disorders. Examples of CNS disorders include, but are not limited to, Parkinson disease; Alzheimer disease, mild cognitive impairment; depression; defective long-term memory; Amyotrophic Lateral Sclerosis (ALS); CNS trauma; hypokinetic disorders; bradykinesia; slowness of movement; paucity of movement; impairment of dexterity; hypophonia; monotonic speech; muscular rigidity; masked faces; decreased blinking; stooped posture; decreased arm swinging when walking; micrographia; parkinsonian tremor; parkinsonian gait; postural instability; festinating gait; motion freezing; disturbances of **cognition,** mood, sensation, sleep or autonomic function; dementia; and sleep disorders.

In a specific embodiment, the central nervous system disorder to be prevented, treated and/or managed is Parkinson disease, Alzheimer disease, mild cognitive impairment, dementia, depression, defective long-term memory, Amyotrophic Lateral Sclerosis (ALS) or CNS trauma.

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In another embodiment of the invention, nonmotor symptoms are treated, prevented or managed using the methods of the invention, including, but not limited to, disorders of mood, **cognition,** defective long-term memory, sensation, sleep, dementia, and depression. In other embodiment of the invention, secondary forms of parkinsonism are treated, prevented or managed by the methods of the invention, including, but not limited to, drug induced parkinsonism, vascular parkinsonism, multiple system atrophy, progressive supranuclear palsy, disorders with primary tau pathology, cortical basal ganglia degeneration, parkinsonism with dementia, hyperkinetic disorders, chorea, Huntington disease, dystonia, Wilson disease, Tourette syndrome, essential tremor, myoclonus, and tardive movement disorders. In other embodiment of the invention, other central nervous system disorders are treated, prevented or managed by the methods of the invention, including, but not limited to, Alzheimer disease, mild cognitive impairment, Amyotrophic Lateral Sclerosis (ALS) and CNS trauma.

(emphasis added)

In view of the above remarks, it is respectfully submitted that applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with no more than routine experimentation. The rejection does not present sufficient reasons to doubt the veracity of the enabling statements set forth in the disclosure. Thus, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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